Prediction factors of tolvaptan effectiveness in patients with refractory ascites complicated with hepatocellular carcinoma

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Objective Tolvaptan (TVP) is an effective treatment for patients with cirrhotic ascites; however, studies have indicated that a sufficient effect is difficult to obtain in patients with hepatocellular carcinoma (HCC). This study evaluates the efficacy of TVP in patients with HCC with refractory ascites.

Methods We retrospectively enrolled 32 patients with liver cirrhosis and refractory ascites [mean age: 74 years (range, 47–86 years), men: 78.1% (25/32)]. All patients had HCC and were treated with TVP at our hospital. A TVP responder was defined as a patient who experienced decrease in body weight by ≥1.5 kg within 1 week of treatment. Univariate and multivariate analyses were performed to evaluate clinical and laboratory predictive factors of TVP response.

Results The TVP response rate was 46.9% (15/32 patients) after 1 week of treatment. HCC treatment (transcatheter arterial chemoembolization and/or radiofrequency ablation) was administered to 11/15 (73.3%) responders. In the multivariate analysis, the reduction of urine osmolality was higher in responders than nonresponders (202 mOsm/l vs. 65 mOsm/l, $P = 0.040$), and the tumor stage ($P = 0.043$) was worse in nonresponders. Multivariate Cox proportional hazards regression analysis indicated a significantly better prognosis among responders than among nonresponders ($P < 0.01$).

Conclusion The HCC tumor stage and the reduction in urine osmolality can predict the efficacy of TVP in patients with refractory ascites complicated with HCC. TVP may allow therapeutic intervention for HCC and improve prognosis, even in patients with Child–Pugh class C. Eur J Gastroenterol Hepatol 33: e161–e166

Introduction

Hepatic edema and ascites are major complications of decompensated liver cirrhosis [1]. Hepatic ascites is refractory in approximately 15–20% of all patients with ascites and does not respond to salt restriction and high-dose diuretic therapy [2]. Patients with refractory ascites can be treated with various therapies, such as concentrated ascites reinfusion therapy, transjugular intrahepatic portosystemic shunt (TIPS), and peritoneovenous shunt [3–5], but the efficacies of these therapies are limited [6]. Refractory ascites is also associated with poor quality of life [7,8].

Tolvaptan (TVP), a vasopressin V2 receptor antagonist, is an effective diuretic for patients with ascites. Inhibition of vasopressin V2 receptor by TVP prevents insertion of aquaporin-2 water channels into the apical cell membrane of the collecting duct, increasing free water excretion without affecting urinary sodium or potassium excretion significantly [9]. This reduces water retention but maintains serum sodium levels, which is a desirable outcome in patients with decompensated liver cirrhosis complicated by refractory ascites. Although several reports have shown the effectiveness of TVP in patients with cirrhosis, the reported effective ratio is 36–63% and prediction of its effectiveness prior to treatment remains challenging [10–15].

Although many patients with cirrhosis have concurrent hepatocellular carcinoma (HCC), only few reports have described the causal relationship between HCC and ascites development. Furthermore, there were limited reports on the influence of HCC on the effectiveness of TVP. A recent study has revealed that ascites in patients with HCC responded less to TVP than ascites in patients without HCC, but the mechanism remains unelucidated [16].

The continuation of HCC treatment is difficult if intractable ascites occurs during the course of treatment; however, treatment can be resumed with successful ascites control in some cases. This study evaluated the efficacy of TVP in patients with refractory ascites complicated with HCC by retrospectively examining the efficacy, predictive factors, and vital prognosis of TVP treatment in such patients.

Methods

Patients

A single-center retrospective study was performed at Saiseikai Niigata Hospital, Niigata, Japan, from January

European Journal of Gastroenterology & Hepatology 2021, 33:e161–e166

Keywords: ascites, diuretic effect, hepatocellular carcinoma, liver cirrhosis, tolvaptan

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Received 28 March 2020 **Accepted** 2 May 2020

2014 to July 2018. We enrolled 32 patients with cirrhosis, refractory ascites, and untreated HCC. The diagnosis of liver cirrhosis was based on laboratory results and computed tomography findings of hepatic cirrhotic appearance, splenomegaly, esophageal varices, and massive ascites. The refractory ascites refers to the ascites, which is inadequately controlled even by the use of existing diuretics such as the loop diuretics and/or anti-aldosterone agents. Cases of positive cytology of ascites and diagnosed as peritoneal dissemination were excluded. Patients who were diagnosed with spontaneous bacterial peritonitis were enrolled in the study if ascites continued to accumulate even after improvement of the infection findings by administration of antibiotics. The exclusion criteria were lack of follow-up data within 1 week. Of the 34 patients initially included in this study, two patients were excluded (one was lost to follow up within 1 week and one had insufficient laboratory data). Therefore, a total of 32 patients (25 men and seven women) aged 47–86 years were included in the final analysis. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Saiseikai Niigata Hospital (Permit number: E17-27). This study was carried out by the opt-out method of our hospital website. Passive consent, commonly termed opt-out consent, assumes agreement to study participation unless consent is deliberately withdrawn.

Study protocol

All the patients were hospitalized for >1 week to receive oral TVP (Samsca; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) and monitor their body weight and the occurrence of adverse events. The daily dose of TVP was either 3.75 or 7.50 mg based on the patient's body weight. The usual dose of TVP for refractory ascites is 7.5 mg, but given the risk of dehydration and hypernatremia associated with excessive diuresis, we used an initial dose of 3.75 mg for patients weighing <60 kg. TVP was continually administered from the time of admission, while the preceding loop diuretics and anti-aldosterone agents were concomitantly given without altering the doses. The patient's water intake was not restricted. Biochemical tests were performed on blood and spot urine samples. The baseline clinical characteristics included age, body weight, BMI, etiology of the cirrhosis, Child–Pugh score, Model for End-Stage Liver Disease (MELD) score, albumin–bilirubin (ALBI) grade, UICC TNM staging (version 8), the Barcelona Clinic Liver Cancer (BCLC) stage, initial dose of diuretic drugs, and laboratory and urinary data obtained just prior to commencing TVP treatment. Urine osmolality was measured before and 4 h after TVP administration. Reduction in urine osmolality was noticed as early as 4 h after TVP administration. Therefore, it was included as a candidate prognostic factor in characteristics.

Evaluation of treatment response

TVP responder was defined as a patient experiencing a decrease of ≥1.5 kg body weight after a week of TVP treatment, while a nonresponder was a patient who did not lose ≥1.5 kg body weight after 1 week of TVP treatment. This definition was used since the change in body weight that most accurately reflected symptom reduction was reported as 1.5 kg/week [17].

Statistical analysis

Data are presented as medians and ranges. Continuous variables of responders and nonresponders were analyzed using the Mann–Whitney *U* test, and categorical variables were analyzed using Fisher's exact test. Univariate and multivariate logistic regression analyses assessed the predictors for improvement of refractory ascites by TVP. The survival rate was estimated using the Kaplan–Meier method and Cox proportional hazards regression analyses. In all analyses, a *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using the EZR software, which is based on R and R commander [18].

Results

Characteristics of patients treated with tolvaptan

The demographics and other baseline characteristics of the 32 patients treated with TVP are shown in Table 1. The median age was 74 years (range 47–86 years) and the median body weight was 63.3 kg (range 45.3–102.1 kg). There were seven women (21.9%) and 25 men in (78.1%) the study cohort. The etiology of cirrhosis included hepatitis B (6/32, 18.8%), hepatitis C (15/32, 46.9%), alcohol (6/32,

Table 1. Baseline characteristics of the 32 cirrhotic patients with refractory ascites and untreated hepatocellular carcinoma

	Variable	Average (range)
Demographics	Age (years)	74 (47–86)
	Sex (male/female)	25/7
	Body weight (kg)	63.3 (45.3–102.1)
	BMI (kg/m^2)	25.2 (18.5–36.6)
	Etiology (HBV/HCV/alcohol/others)	6/15/6/5
	Child–Pugh class (A/B/C)	0/11/21
	Child–Pugh score (points)	10.0 (8–13)
	MELD score (points)	13.5 (6–24)
	ALBI grade (1/2/3)	0/9/23
Laboratory data	Serum albumin (g/dl)	2.5 (1.8–3.6)
	Total bilirubin (mg/dl)	1.97 (0.43–17.19)
	Prothrombin time (%)	65.0 (26.9–105.9)
	Blood urea nitrogen (mg/dl)	26.7 (11.9–80.2)
	Serum creatinine (mg/dl)	1.06 (0.53–4.45)
	eGFR (ml/min)	43.8 (11.6–116.1)
	NH_3 (mg/dl)	61 (20–199)
	Serum Na (mEq/l)	133.5 (125–143)
	Serum osmolality (mOsm/l)	284 (262–305)
	Urine osmolality (mOsm/l)	443 (269–742)
	Alpha-fetoprotein (mg/ml)	320 (1–376514)
	Des-γ-carboxy prothrombin (mAU/ml)	361 (10–75000)
	Platelet count (×10^3/μl)	10.2 (1.9–36.2)
Initial dose of diuretic drugs	Tolvaptan (3.75/7.50 mg/day)	10/22
	Furosemide (mg/day)	20 (0–80)
	Spironolactone (mg/day)	25 (0–75)
Tumor-related factors	UICC TNM stage (I/II/III/IV)	7/12/9/4
	UICC T-factor (1/2/3/4)	7/12/12/1
	Portal vein tumor thrombus (Vp0/1/2/3/4)	25/0/0/2/5
	Extrahepatic tumor spread (yes/no)	4/28
	BCLC staging (A/B/C/D)	3/5/3/21

ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; UICC, Union for International Cancer Control.

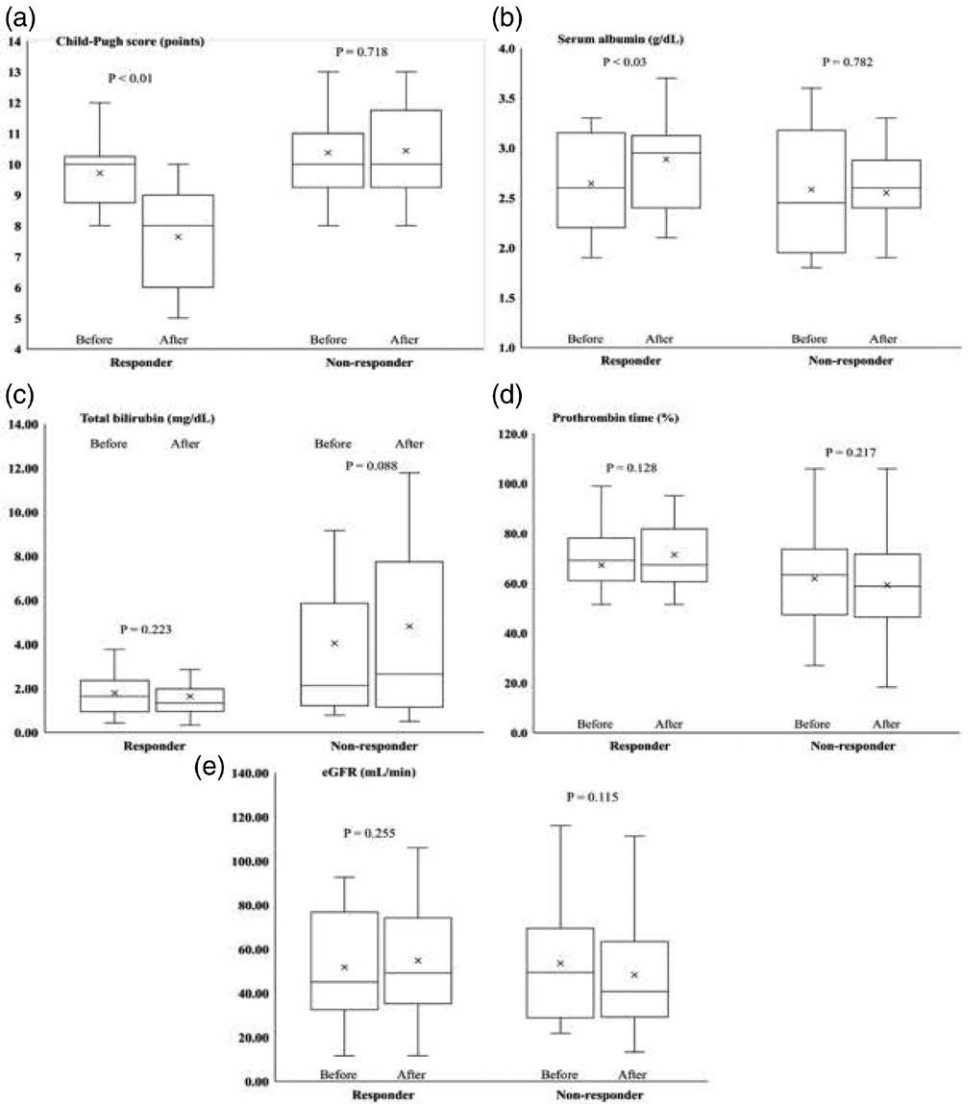

Fig. 1. Comparison of liver functional parameters before and after tolvaptan (TVP) administration: (a) Child-Pugh score; (b) serum albumin; (c) total bilirubin; (d) Prothrombin time; (e) eGFR (estimated glomerular filtration rate). *P*-values <0.05 were considered statistically significant.

18.8%), and other causes (5/32, 15.6%). The percentage of patients with Child–Pugh class A, B, and C was 0% (0/32), 34.4% (11/32), and 65.6% (21/32), respectively. There were 13 patients (40.6%) with advanced HCC, defined as TNM stage III or IV. The percentage of patients with the BCLC stage A, B, C, and D was 9.4% (3/32), 15.6% (5/32), 9.4% (3/32), and 65.6% (21/32), respectively. The median daily dose of furosemide was 20 mg (range, 0–80 mg) and that of spironolactone was 25 mg (range, 0–75 mg). The starting dose of TVP was 3.75 mg/day for 10 patients (31.3%) and 7.50 mg/day for the remaining 22 patients.

Clinical effects

We evaluated the clinical effects of TVP treatment in the responders. The response rate to TVP was 46.9% (15/32 patients) after 1 week of treatment. The median reduction in body weight was 3.0 kg (range, 2.0–6.4 kg) among responders and 0.2 kg (range, 0.0–1.8 kg) among non-responders ($P < 0.01$) (Table 1). The 24-h urine volume after TVP administration was significantly higher among responders than among nonresponders (2240 ml vs. 1153 ml, $P < 0.01$). The median duration of oral TVP was 299 days (21–1546 days) in the responders. Comparison of liver functional parameters before and 1 month after TVP administration showed significant improvement in Child-Pugh score and serum albumin in responders but no change in nonresponders (Fig. 1). Because residual liver function was improved, treatment for HCC was provided in 11/15 of the responders (73.3%). Transcatheter arterial chemoembolization (TACE) was given to nine patients and radiofrequency ablation (RFA) to nine patients (with duplication). The median number of TACE performed was two times (1–5 times), and the median number of RFA was two times (1–4 times). The therapeutic response of initial treatment (TACE and/or RFA) was complete response in six patients, partial response in three patients, and stable disease in two patients. During the observation period, 20 patients died, all of whom died from liver-related disease (HCC and liver failure). There was no difference in the cause of death between responders and nonresponders.

Comparison of tolvaptan effectiveness

To reveal the characteristics of TVP responders, the demographics and blood and urine data obtained prior to TVP

Table 2. Comparison of baseline characteristics between tolvaptan responder and nonresponders

	Variable	Responders (n = 15)	Nonresponders (n = 17)	*P*-value
Demographics	Age (years)	74 (47–84)	78 (56–86)	0.571
	Sex (male/female)	11/4	14/3	0.424
	Body weight (kg)	66.0 (45.3–102.1)	60.9 (47.6–84.2)	0.332
	Reduction in body weight (kg)	3.0 (2.0–6.4)	0.2 (0.0–1.8)	<0.01*
	BMI (kg/m^2)	25.6 (20.7–36.6)	23.9 (18.5–29.7)	0.218
	Etiology (HBV/HCV/alcohol/others)	3/6/2/4	3/9/4/1	0.399
	Child–Pugh class (B/C)	6/9	5/12	0.398
	Child–Pugh score (points)	10 (8–12)	10 (8–13)	0.450
	MELD score (points)	12 (6–21)	16 (7–24)	0.290
	ALBI grade (2/3)	5/10	4/13	0.411
Laboratory data	Serum albumin (g/dl)	2.5 (1.9–3.3)	2.5 (1.8–3.6)	0.806
	Total bilirubin (mg/dl)	1.71 (0.43–3.77)	2.10 (0.78–17.19)	0.180
	Prothrombin time (%)	69.1 (27.4–99.0)	63.5 (26.9–105.9)	0.509
	Blood urea nitrogen (mg/dl)	26.3 (13.6–68.8)	27.0 (11.9–80.2)	0.678
	Serum creatinine (mg/dl)	1.03 (0.61–4.45)	1.26 (0.53–2.40)	0.720
	eGFR (ml/min)	42.1 (11.6–99.7)	45.5 (21.8–116.1)	0.763
	NH_3 (mg/dl)	52 (20–123)	62 (22–199)	0.752
	Serum Na (mEq/l)	135 (126–143)	132 (125–143)	0.126
	Serum osmolality (mOsm/l)	285 (280–300)	284 (262–305)	0.216
	Urine osmolality (mOsm/l)	464 (269–742)	421 (339–659)	0.756
	Reduction of urine osmolality (mOsm/l)	202 (69–511)	65 (2–418)	0.022*
	Alpha-fetoprotein (mg/ml)	63 (3–3379)	508 (1–376515)	0.126
	Des-γ-carboxy prothrombin (mAU/ml)	633 (17–54972)	137 (10–75000)	0.533
	Platelet count (×10^3/μl)	9.5 (4.0–16.2)	12.9 (1.9–36.2)	0.637
Initial dose of diuretic drugs	Tolvaptan (3.75/7.50 mg/day)	4/11	6/11	0.445
	Furosemide (mg/day)	10 (0–40)	20 (0–80)	0.193
	Spironolactone (mg/day)	25 (0–75)	25 (0–50)	0.290
Tumor-related factors	UICC TNM stage (I–II/III–IV)	12/3	7/10	0.030*
	UICC T-factor (1–2/3–4)	12/3	7/10	0.030*
	Portal vein tumor thrombus (yes/no)	1/14	6/11	0.061
	Extrahepatic tumor spread (yes/no)	0/15	4/12	0.058
	BCLC staging A–C/D	6/9	5/12	0.398

P-values <0.05 were considered statistically significant.
ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; UICC, Union for International Cancer Control.

treatment were compared between the responders and nonresponders (Table 2). In the univariate analysis, there were no significant differences in age, sex, body weight, etiology of the cirrhosis, Child–Pugh score, MELD score, ALBI grade, the initial dose of diuretic drugs, hepatic function, renal function, or other blood data between responders and nonresponders. Furthermore, there was no significant difference in urine osmolality levels. However, a reduction in urine osmolality was significantly higher among responders than among nonresponders (202 mOsm/l vs. 65 mOsm/l, $P = 0.022$) (Fig. 2). In the univariate analysis, HCC progress (i.e., the tumor stage) and the T-factor (both $P = 0.030$) were worse in nonresponders than in responders (Table 2). A multivariate regression analysis performed to evaluate the factors that were significant in the univariate analysis (Table 3) revealed that a reduction in urine osmolality ($P = 0.040$) and the tumor stage ($P = 0.043$) were positively correlated with an improvement of refractory ascites.

Cumulative survival rate

We used multivariate Cox proportional hazards regression analysis to compare the cumulative survival rate between responders and nonresponders (Fig. 3). The analysis revealed that responders had a significantly better prognosis than nonresponders ($P < 0.01$). Furthermore, significant differences of prognosis were identified, even when we limited the variables to tumor stage I or II ($P < 0.01$) (Fig. 4).

Discussion

Several factors, such as serum urea nitrogen, serum creatinine, urinary urea nitrogen excretion, urinary sodium excretion, urinary Na/K ratio, reduction of urine osmolality, and complication of HCC, have been considered as the predictors of TVP response among patients with cirrhosis [11–14,19–21]. Although TVP has been reported to be ineffective in patients with refractory ascites complicated with HCC, few studies have examined the predictors of TVP efficacy in patients with HCC. Ohki *et al*. [11] reported that there were significant differences in TVP effectiveness related to uncontrolled liver neoplasms. In our study of patients with hepatic ascites complicated by HCC, tumor stage and urine osmolality reduction were identified as predictive factors of TVP effectiveness using multivariate analysis. Urine osmolality reduces due to the efficacy of TVP and can be included as a predictor as it can predict the treatment effect as early as 4 h after treatment initiation.

TVP, an antagonist of vasopressin type 2 receptor, inhibits water reabsorption and promotes the excretion of free water without increasing sodium excretion. The mechanism of its diuretic action is different from that of conventional diuretics that promote sodium diuresis. Clinical trials in Japan have confirmed the efficacy of TVP for refractory ascites regardless of the serum albumin level [22]. In 2013, TVP was approved for use in combination with conventional diuretics for refractory ascites in Japan [23]. In 2015, the Japanese Society of Gastroenterology recommended the use of TVP prior to the intravenous administration of diuretics or albumin, large-volume

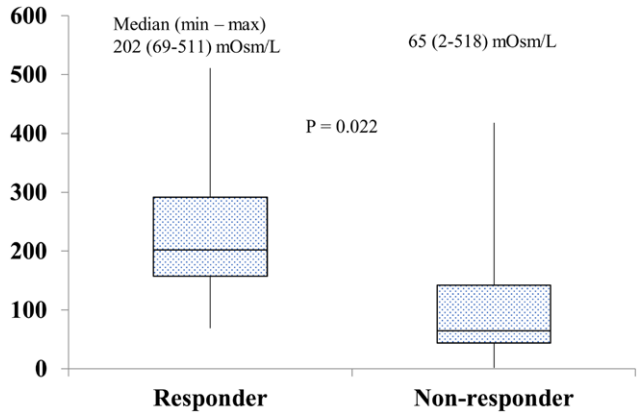

Fig. 2. Comparison of the reduction in urine osmolality between tolvaptan responders and nonresponders. *P*-values <0.05 were considered statistically significant.

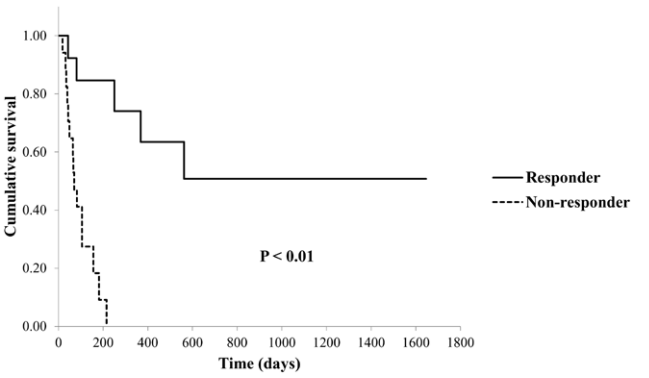

Fig. 3. Kaplan–Meier curves for tolvaptan responders (solid line) and nonresponders (dotted line). Significant differences were analyzed by Cox proportional hazards regression analysis. *P*-values <0.05 were considered statistically significant.

Table 3. Multivariate regression analysis assessing the effectiveness of tolvaptan

Variable	OR (95% CI)	*P*-value
Reduction of urine osmolality (mOsm/l)	1.007 (1.004–1.014)	0.040*
UICC stage	0.341 (0.120–0.967)	0.043*
UICC T-factor	0.332 (0.108–1.022)	0.055*

P-values <0.05 were considered statistically significant.
CI, confidence interval; OR, odds ratio; UICC, Union for International Cancer Control.

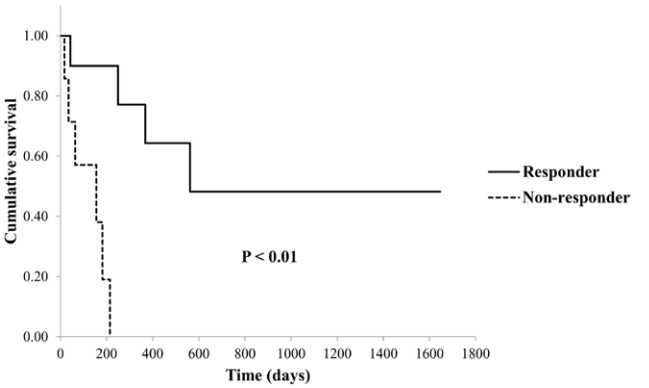

Fig. 4. Kaplan–Meier curves for responders (solid line) and nonresponder (dotted line) to tolvaptan, limited to tumor stage I or II. Significant differences were analyzed by Cox proportional hazards regression analysis. *P*-values <0.05 were considered statistically significant.

paracentesis, TIPS, or peritoneovenous shunting [24]. Furthermore, following the approval of TVP, early administration of TVP has been recommended before increasing furosemide or spironolactone dosage [24]. This study aimed to evaluate the efficacy of TVP in patients with HCC complicated by refractory ascites.

A clinical study has demonstrated the effectiveness of TVP in patients with a urine osmolality of >352 mOsm/l prior to TVP administration, showing decreased urine osmolality of >26% after 4–6 h [8,25]. For patients with liver cirrhosis, a reduction in urine osmolality of >25% has been positively correlated with an improvement in refractory ascites [11]. Determination of urine osmolality 4 h after TVP administration predicts the subsequent efficacy and appropriate dosage of TVP [26]. This correlation is due to decreased urine osmolality and increased free water clearance after TVP treatment and is consistent with the antagonism of renal V2 vasopressin receptors [27]. In other words, a diuretic effect may be expected as the urine osmolality decreases after the oral administration of TVP. Although our study was conducted in patients with HCC, it has been suggested that the efficacy of TVP can be predicted by measuring the degree of reduction in urine osmolality in patients without HCC.

Portal hypertension associated with the microinvasion of HCC is considered as an important cause of pathogenesis of ascites in HCC. Pawlik *et al*. [28] showed that the incidence of microscopic vascular invasion was 31% for all tumors measuring ≤5 cm compared with 55% for all tumors measuring 5.1–6.5 cm. Chen *et al*. [29] found that macrovascular and microvascular invasion were independent factors associated with the development of ascites in patients with HCC caused by hepatitis B virus. Nakagawa *et al*. [30] reported that the progression of portal hypertension attenuated the effect of TVP. These findings indicate that ascites accumulation following HCC progression is mainly caused by portal hypertension subsequent to vascular invasion. In our study, according to the univariate analysis, TVP nonresponders had higher tumor stage T-factors than TVP responders. Therefore, vascular invasion and increased portal hypertension may have triggered ascites development in many patients with HCC.

Some reports have indicated that TVP treatment improves the vital prognosis in patients with liver cirrhosis [12,26]. Although our study was conducted in patients with HCC, the responder group had a significantly better vital prognosis than the nonresponder group. However, in this study, the proportion of patients with tumor stage III or IV was lower in the responder group than in the nonresponder group, suggesting that sampling bias may occur in the comparison of vital prognosis. Therefore, we reviewed the vital prognosis of patients with tumor stage I or II only, with the responder group exhibiting a favorable vital prognosis. In most responders, the reduction of ascites allowed retreatment of HCC and control of HCC appeared to improve the prognosis. In patients with HCC complications, the TVP efficacy has been reported to be poor [11,16]. However, our study indicated that when TVP was effective, HCC could be retreated, thereby improving the prognosis. Therefore, the introduction of TVP should be considered with the

aim of HCC retreatment rather than simply moving to the best supportive care. Higher efficacy of TVP was seen in patients with a high rate of decrease in urine osmolality 4 h after administration, suggesting that the measurement of urine osmolality gradient may predict therapeutic response.

This study had some limitations. First, this was a single-center, retrospective observational study. Second, the sample size was small. A future prospective study including a large number of patients with HCC and ascites from various institutions is necessary to confirm our findings.

In conclusion, the HCC tumor stage and the reduction in urine osmolality are predictive factors of TVP efficacy in patients with refractory hepatic ascites complicated with HCC. TVP may improve survival outcomes for patients with liver cirrhosis and HCC, even in patients with Child–Pugh class C.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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